PATHOGENESIS AND MORBIDITY OF AUTOANTIBODY SYNDROMES IN WALDENSTRÖM'S MACROGLOBULINEMIA

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Autoimmune disorders in WM include chronic cold agglutinin disease (CAD), mixed cryoglobulinemia (MC) and immune-mediated polyneuropathy (IP). In all 3 syndromes, the patients "tell you" what they have. A number of autoantigenic specificities have been described that react with monoclonal IgMs. It may be important to distinguish between autoimmune and autoreactive. Perhaps 10-20% of WM IgMs have definable antibody activity but this may be a low figure. Epidemiologic data suggest that infection/inflammation is associated with chronic antigenic stimulation in some patients who develop plasma cell dyscrasias. MGUS precedes WM in many patients just as it appears to consistently precede myeloma. Most patients with autoimmune IgM-related diseases would be classified as having MGUS were it not for the consequences of antigen-antibody combination. However, other patients have frank WM.

Criteria for antibody activity of paraproteins can be rigorously defined. In considering the frequency of monoclonal proteins with antibody activity, the question arises as to how many potential antigens exist. This is probably a very large number; somewhere between 10^9 and 10^{12}. The principal problem is detection but new methods have been described which may aid in identifying M-proteins with antibody activity. If initiated by antigen, it is unclear whether the immune response begins as a polyclonal process which then becomes monoclonal and autonomous. Alternatively, some antigens may elicit monoclonal antibody responses from the outset.

Prototype patients will be described to illustrate the autoimmune aspects of CAD, MC, and IP. Some of these "autoimmune" disorders may actually represent cross-reactions to exogenous substances. Whatever the putative antigen, there is no doubt that binding of autoantigen to monoclonal IgM results in clinical sequelae. These patients present at an earlier stage than WM patients who do not have evident antibody activity. Diagnosis is often delayed in patients with these autoimmune manifestations because of the small size of their "dangerous" B cell clone. Thus the natural history and clinical presentation of patients with autoimmune-mediated IgM-related syndromes are distinct. Prompt recognition of signs and symptoms is imperative for correct diagnosis and institution of effective treatment.